
Tetrakis(hydroxymethyl) phosphonium chloride as a covalent cross-linking agent for cell encapsulation within protein-based hydrogels.

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Public Summary:

Native tissues provide cells with complex, three-dimensional (3D) environments comprised of hydrated networks of extracellular matrix proteins and sugars. By mimicking the dimensionality of native tissue while deconstructing the effects of environmental parameters, protein-based hydrogels serve as attractive, in vitro platforms to investigate cell-matrix interactions. For cell encapsulation, the process of hydrogel formation through physical or covalent cross-linking must be mild and cell compatible. While many chemical cross-linkers are commercially available for hydrogel formation, only a subset are cytocompatible; therefore, the identification of new and reliable cytocompatible cross-linkers allows for greater flexibility of hydrogel design for cell encapsulation applications. Here, we introduce tetrakis(hydroxymethyl) phosphonium chloride (THPC) as an inexpensive, amine-reactive, aqueous cross-linker for 3D cell encapsulation in protein-based hydrogels.

Scientific Abstract:

Native tissues provide cells with complex, three-dimensional (3D) environments comprised of hydrated networks of extracellular matrix proteins and sugars. By mimicking the dimensionality of native tissue while deconstructing the effects of environmental parameters, protein-based hydrogels serve as attractive, in vitro platforms to investigate cell-matrix interactions. For cell encapsulation, the process of hydrogel formation through physical or covalent cross-linking must be mild and cell compatible. While many chemical cross-linkers are commercially available for hydrogel formation, only a subset are cytocompatible; therefore, the identification of new and reliable cytocompatible cross-linkers allows for greater flexibility of hydrogel design for cell encapsulation applications. Here, we introduce tetrakis(hydroxymethyl) phosphonium chloride (THPC) as an inexpensive, amine-reactive, aqueous cross-linker for 3D cell encapsulation in protein-based hydrogels. We characterize the THPC-amine reaction by demonstrating THPC's ability to react with primary and secondary amines of various amino acids. In addition, we demonstrate the utility of THPC to tune hydrogel gelation time (6.7 ± 0.2 to 27 ± 1.2 min) and mechanical properties (storage moduli approximately 250 Pa to approximately 2200 Pa) with a recombinant elastin-like protein. Lastly, we show cytocompatibility of THPC for cell encapsulation with two cell types, embryonic stem cells and neuronal cells, where cells exhibited the ability to differentiate and grow in elastin-like protein hydrogels. The primary goal of this communication is to report the identification and utility of tetrakis(hydroxymethyl) phosphonium chloride (THPC) as an inexpensive but widely applicable cross-linker for protein-based materials.

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